given to them, and in most cases there was no difficulty in obtaining their strict co-operation. It was usual also to inform them before starting that the treatment was likely to take some time before good results could be expected.

The investigation of these sixteen cases showed that ketogenic diet is an unsuitable form of treatment for out-patients. Accurate preparation and administration of the diet was essential if the urinary *p*H was to be kept steadily at low levels. Two patients who were not taking the diet strictly, and which would be representative of the average out-patient receiving treatment without supervision, produced very irregular and high *p*H values, which were not contributive to success.

CONCLUSIONS

Sixteen cases of infection of the urinary tract treated with ketogenic diet are discussed.

1. Ketogenic diet had the effect of increasing the hydrogen-ion concentration of the urine in all cases except one. The effect on the urinary *p*H was characterized by a rapid initial fall, and a maintained low general level lasting till the end of the third week, when there was a tendency for the *p*H to become irregular and to stand at a slightly higher level.

2. Acetone bodies were produced in the urine in all cases, but varying greatly in amount in individual cases. Acetone appeared in greatest amount during the first five days after the *p*H had fallen, and by the end of three weeks had become very much diminished.

3. Five cases were cured completely by treatment with ketogenic diet. In these cases the urinary figure was maintained about *p*H 5.4 and acetone bodies were produced in satisfactory quantity. Four cases were cured following the addition of ammonium nitrate to the treatment. Two cases were cured following the addition of hexamine to the treatment. Five cases were improved, but the urines were not sterile. Of these, three left hospital before treatment was completed ; one was suffering from a subacute condition which interfered with metabolism ; and one failed completely to take the diet.

4. Treatment with ketogenic diet improved the symptoms and the characters of the urine rapidly. No symptoms were caused by the hyperacid urine.

5. It was found desirable to increase the diet by stages according to the ketogenic-anti-ketogenic ratio, in order to avoid nausea and vomiting. Only a single case had any gastric upset.

6. Two cases were nursing mothers. The milk was found to be of normal composition, and no gastro-intestinal symptoms were shown by the babies.

7. Every patient was in excellent health on discharge from hospital.

8. The results suggested that ketogenic diet was an unsuitable form of treatment for out-patient departments.

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ERYTHEMA NODOSUM

BY

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Three divergent views are to be found in the literature regarding the aetiology of erythema nodosum.

1. *The Rheumatic.*—Following the work of Mackenzie[1] some fifty years ago the theory that erythema nodosum was associated with the acute rheumatic process was formulated. This view was supported by clinical evidence which showed that certain cases of the disease were preceded by acute tonsillitis of the streptococcal type, associated with polyarthritis and sometimes followed by rheumatic valvular disease of the heart. The exact relation was never clearly defined. However, this view got into the English textbooks, where it has remained until the present day.

2. *The Tuberculous.*—For many years Continental workers have called attention to the fact that certain cases of erythema nodosum are closely associated with tuberculosis. Recently, due chiefly to the careful work of the Scandinavian school—particularly to the researches of Wallgren[2] and Ernberg[3]—the connexion between the disease and tuberculosis has been largely explained. These workers have shown that the great majority (95 per cent.) of patients with erythema nodosum are strongly positive to tuberculin, that tubercle bacilli may be found by the gastric lavage method in a high percentage of cases, that *x*-ray skiagrams of the chest reveal primary lung and hilus lesions in the majority of cases, and that a fair number of patients who have suffered from the disease develop frank tuberculous lesions within a year of the attack. They consider that erythema nodosum is a manifestation of primary tuberculous infection, such as phlycternular conjunctivitis, " benign infiltration of the lung," and early pleurisy, which conditions they term " paratuberculous."

3. *The Acute Specific Disease.*—Neither the rheumatic nor the tuberculous school have ever been able to claim all the cases ; hence Trousseau,[4] Lendon,[5] and Symes[6] put forward the view, at different times, that the disease was essentially an acute specific fever. Their arguments were plausible, and many were inclined to accept their views, including such careful clinical observers as Robert Hutchison. Their theory was based, however, on mere deduction, and was supported by no experimental evidence. A variation of this view was put forward more recently by Fornara,[7] who suggested that the disease was caused by a specific virus, but that the actual eruption only occurred when the patient was in a state of allergy to the tubercle bacillus.

AUTHOR'S OBSERVATIONS

Some two years ago I[8] published the result of certain investigations which had led me to conclude that " erythema nodosum is a type of hyper-reactive tissue response to different bacterial allergens, and that the allergens responsible for the disease in London are commonly tuberculin and haemolytic streptococcal endotoxin." The table given below, and reprinted, with permission from the *Quarterly Journal of Medicine*, gives in the briefest space the facts upon which this deduction was made.

The cases are seen to fall into two groups. The first five belong to the tuberculous type, the latter three to the streptococcal or rheumatic type. In the first group

all the patients are seen to be strongly positive to tuberculin and negative to the streptococcal extract; *x*-ray examination revealed lung lesions, tubercle bacilli were found in the gastric lavage in three out of five, and all gave a history of tuberculous contact in the home. While in the second group all were negative to tuberculin and positive to haemolytic streptococcal extract, gave *no* history of contact, showed *no* lung lesions, and had a negative gastric lavage, in all these the attack was preceded by an acute pharyngitis of the streptococcal type and was accompanied by polyarthritis. Besides these cases certain further experiments were also reported—for example, a case was described in which erythema nodosum was twice produced in the same individual (a contact tuberculous patient) by the subcutaneous injection of old tuberculin; in another case (of the streptococcal type) the eruption was produced locally by the intradermal and subcutaneous injection of streptococcal extract.

TABLE I

Case No.	Sex	Age (years)	Skin Tests: Mantoux	Skin Tests: Haem. Strept Endotoxin	X ray of Chest	Guinea-pig Inoculation	Family History of Tuberculosis	Past History of Rheumatism or Tuberculosis	No of Attack of Erythema Nodosum	Type of Lesion	Throat Infection Preceding Attack	Joint Pains	Type
1	F.	3½	+++	0	Gross hilar shadows	Tuberculosis in three weeks	Mother, phthisis	Nil	First	Few small	Nil	Nil	Tuberculous
2	F.	5½	+++	0	Gross hilar shadows	Tuberculosis in six weeks	Mother, phthisis	Nil	First	Very few small	Nil	Nil	Tuberculous
3	F.	5½	+++	0	Definite hilar shadows	Nil	Mother, phthisis	Nil	First	Many small	Nil	Nil	Tuberculous
4	F.	13	+++	0	Suggestive enlargement	Nil	Mother, phthisis	Nil	First	Moderate	Nil	Nil	Tuberculous
5	F.	7	+++	+	Lung consolidation	Tuberculosis in six weeks	Aunt, phthisis	Nil	First	Small	Nil	Nil	Tuberculous
6	F.	10	0	+++	Normal	Nil	Nil	Sub-acute rheumatism, three years	Fifth	Few large indurated	Present	Severe	Streptococcal
7	F.	9	0	+++	Insignificant hilar shadows	Nil	Nil	Nil	Second	Large diffuse	Present	Present	Streptococcal
8	F.	8	0	+++	Normal	—	Nil	Rheumatic pains for one month previously	First	Large indurated	Present	Severe	Streptococcal

+++ = very strong positive. 0 = no reaction. + = weak positive reaction.

The publication of this report raised a number of inquiries. It was asked (1) whether the organisms in the gastric lavage were human or bovine in type; (2) how valuable and reliable the gastric lavage method was to be considered; (3) what was the prognosis in erythema nodosum, especially the tuberculous type. A report dealing exhaustively with these points was published by me in collaboration with Dr. Brockington[9] in January, 1933. The report may be summarized as follows.

The deposit of the gastric lavage from seventy children was inoculated into guinea-pigs. Tubercle bacilli were obtained in five out of seventeen cases of erythema nodosum, in three out of seven cases of generalized tuberculosis, in three out of eleven cases of suspected tuberculosis, in one out of seventeen contact cases, and in none out of eighteen control cases. Dr. Stanley Griffith typed nine of the strains obtained, all being of the human type except one, which was recovered from a case of tuberculous peritonitis which had become generalized. The results of this investigation, together with a study of the literature, permitted us to conclude that the gastric lavage method is reliable and useful. A further study of the subsequent history of patients with erythema nodosum of the tuberculous type led us to agree with the teaching of the Continental schools that erythema nodosum may be part of the primary complex of tuberculous infection, and that hence the prognosis depends very largely on the line of treatment followed. If such patients are rested for a period of months, have good food and fresh air, and are protected from infection, the prognosis is extremely good. If, however, they are allowed to continue strenuous work, are exposed to intercurrent infection, or live in unhealthy surroundings, the prognosis is grave and the tuberculous process tends to spread and become generalized.

The present report follows directly on the two quoted above, and gives the number and percentages of the different types of erythema nodosum as found in London and Dublin up to date. Using the methods described above, thirty-eight patients with erythema nodosum were investigated in London and eleven in Dublin.

TABLE II.—*Incidence of Erythema Nodosum Types*

	London		Dublin	
	Number	Percentage	Number	Percentage
Tuberculous	27	71	10	90.9
Streptococcal	7	18.4	1	9.1
Indefinite	4	10.6	—	—

If the above table is studied it will be found that in London 71 per cent. of the patients were classified as tuberculous, 18.4 per cent. as rheumatic (streptococcal), and 10.6 per cent. as indefinite, while in Dublin up to the present all but one questionable case have been found to belong to the definitely tuberculous type. The higher percentage of the tuberculous type in Dublin is partly explained by the recognized fact that tuberculosis is extremely common in Ireland, while rheumatic infection of all kinds is particularly common in London. Also, the London streptococcal figure may be unduly high owing to the fact that I was engaged in an investigation into the cause of rheumatic fever when collecting the material for this report.

Of the group given in the table termed "indefinite," three of the cases were equally positive to tuberculin and streptococcal extract, and the other tests either could not be done or were indefinite; hence a clear diagnosis was impossible. The fourth case was that of an adult aged 21 years. He gave a mildly positive tuberculin test, but showed no other signs of tuberculosis. He was also "skin-tested" to extracts from a strain of *Streptococcus viridans*, gamma streptococcus, staphylococcus, pneumococcus, and *B. coli*. All these tests gave negative results except the *B. coli* extract, to which the patient was remarkably sensitive. A possible significant fact in this case was a history of acute dysenteric infection some time previously. Though further detailed investigations are necessary in such cases before it may be more than tentatively suggested that other organisms beside the haemolytic streptococcus and the tubercle bacillus may cause the syndrome of erythema nodosum, the following case suggests that this is probably so.

CASE I

A girl, aged (?) 12 years, had a rigor and vomited on January 8th, 1932. Next day "spots" were noticed on the trunk. On January 13th she was able to return to school; on the 25th she had another rigor and "rash" on the trunk. On the 31st she complained of sore throat, and on February 1st was admitted to hospital. The patient had no definite complaint, but there was present an eruption on the legs, arms, abdomen, and back, in type being similar to that of erythema nodosum, except that the individual lesions were smaller. Tests for typhoid, paratyphoid, and undulant fever were negative.

On February 8th the eruption was more marked; on the 17th she complained of headache, and on the 18th of pain in the neck and photophobia, and vomited. Skin reactions to Dick streptococcal extract and tuberculin were negative. On February 19th meningococci were found in the cerebro-spinal fluid. She was treated by intrathecal, intramuscular, and intravenous injections of antimeningococcal serum. On April 6th she was discharged well. (The above case is published by kind permission of Dr. Troup, Municipal Hospital, Neasden.)

Dr. Robert Hutchison has described a similar case, in which an eruption indistinguishable from erythema nodosum was observed in a case of meningococcal infection. Such cases are medical curiosities, however, and are only of academic importance.

The present report amply supports the original view of the aetiology of erythema nodosum submitted in my first paper on the subject. For instance, after I moved to Dublin the gastric lavage method was continued, and it is noteworthy that the first two cases of the disease thus examined showed tubercle bacilli in their sputa, and both subsequently developed pleurisy. Equally confirmatory evidence in support of the view that certain cases are caused by streptococcal infection was given by a number of case histories, among which were the following.

CASE II

A girl, aged 10 years (previously reported as Case 6, Table I), developed a sixth attack of erythema nodosum in March, 1932. This attack was preceded, as before, by a very acute pharyngitis, throat culture yielding a pure growth of haemolytic streptococci. Skin tests before, during, and after the attack were again negative to tuberculin, while the intradermal injection of haemolytic streptococcal extract gave a very marked reaction, producing a lesion indistinguishable from the spontaneous node of the disease, took a week to fade, and left a bruised appearance of the skin.

CASE III

A woman, aged 50 years, who was suffering from a severe attack of the disease, was investigated in University College Hospital at the request of Sir Thomas Lewis. The eruption was of the large variety, covered all the extensor surface of the legs, was also present on the arms, and was associated with a polyarthritis particularly involving the ankle- and knee-joints. She stated that she had had a previous attack some thirty years before, and that the present attack was associated with an acute sore throat. Throat culture yielded a pure growth of haemolytic streptococci; skin tests gave a negative tuberculin and a strongly positive haemolytic streptococcal reaction. The latter injection produced a rise of temperature and a recrudescence of the eruption and polyarthritis.

The haemolytic streptococcal "endotoxin" (extract) was sent from our laboratory to certain investigators at their request, among whom were Dr. Wallgren of Göteberg and Dr. Symes of Bristol, who have given permission for the publication of the following facts. Dr. Wallgren tested sixty-two children suffering from the disease with tuberculin and haemolytic streptococcal extract. All but five patients gave positive reactions to tuberculin, and these five were positive to the streptococcal extract; twenty-six were positive to both (no further details were given). Dr. Symes sent reports of four adult cases tested to haemolytic streptococcal extract: two were negative and two were positive. One of the negative cases clearly belonged to the tuberculous group, as subsequently she developed frank tuberculous symptoms. The other negative case was indefinite. The two positive cases are worth quoting in detail.

CASE IV

A medical woman, with a history of four previous attacks of erythema nodosum and occasionally nodes on the legs between attacks, was inoculated with haemolytic streptococcal extract, and within twenty-four hours had a severe typical reaction. At the end of forty-eight hours there was an enormous node at the site of inoculation on the leg, and she thought she would have to lie up; however, it then began to subside. She had infected tonsils.

CASE V

A woman admitted to hospital suffering from appendicitis: a very septic appendix was found at operation. A week later she developed the eruption on the legs (quite typical), slight fever, and inoculation with streptococcal extract gave a typical reaction in twenty-four hours. It was still evident at the end of forty-eight hours.

DISCUSSION

The present report confirms the view previously submitted that the disease syndrome of erythema nodosum may be brought about by more than one allergen. It is necessary to stress the finding, however, that by far the commonest cause is tuberculous infection. Indeed, the streptococcal type is extremely rare, and even in London, where streptococcal infection is common, it is doubtful if more than 15 per cent. can be placed in this group. It is not too much to say dogmatically that our attitude to erythema nodosum should be to regard every case as tuberculous till proved otherwise. The importance of this attitude has again and again been borne out by different cases in the above series. For instance, a girl, aged 10, was admitted to the ward with erythema nodosum, diagnosed, as usual, as acute rheumatism. Investigation showed, however, that she belonged to the tuberculous type, tubercle bacilli being found in her sputum. The mother denied all possible family contact infection. Examination of the whole family revealed subsequently that a brother, aged 17, was suffering from a progressive phthisical lesion (he died of tuberculosis later), and also a younger sister had a primary tuberculous lung lesion and a positive sputum. It is often difficult to locate the source of infection, and the physician may meet with angry denials which cover family secrets, only later to be proved correct in his suspicions.

From the academic point of view, the fact that the disease syndrome, with its prodromal period, febrile reaction, eruption, etc., can be brought about by different infections, provided the body is in a state of specific hypersensitiveness to the causal organism, is of very great theoretical importance to those studying bacterial allergy and its relation to immunity. Broadly speaking, it may be said to support the hypothesis as propounded by Rich that allergy is not part of a protective immune process, but a harmful tissue over-reaction. Possibly the suggestion once put forward to me by Professor Okell is nearest the truth—that such allergic reactions are a tissue response occurring in the evolution of immunity, which may be taking place too rapidly in the modern urbanized world for immediate correct adjustment.

My thanks are due to the staff of the Hospital for Sick Children at Great Ormond Street, London, for allowing me to quote their cases and for facilitating this investigation; particularly I wish to thank Dr. Robert Hutchison for his advice and encouragement. I also wish to thank my Dublin colleagues for sending me cases for investigation, especially

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RELATION BETWEEN RENAL HISTOLOGY AND THE CLINICAL PICTURE IN NEPHRITIS

BY

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All attempts to correlate histological changes in the kidneys with clinical symptoms involve the preliminary acceptance of some particular theory of renal function. In this paper the filtration-reabsorption theory of Cushny has been used as a basis. There are difficulties in the unqualified acceptance of this view, but they do not seem to be insurmountable, and the theory accords sufficiently well with both physiological and pathological considerations to suggest that it is, at least in the main, correct. While glomeruli, tubules, interstitium, and vessels are all affected in nephritis, it appears likely that the *glomerular* changes are at all stages the most important.

ACUTE AND SUBACUTE NEPHRITIS

The histological changes in the glomeruli in acute and subacute nephritis are such that we can postulate two main effects on their function. In the first place, only a smaller amount of blood than the normal can circulate through a given tuft per unit of time; and, secondly, the filtration through it must be less selective. The individual glomerulus cannot permit a normal amount of filtration, since insufficient blood passes through it; and the filter permits the passage not only of crystalloids, but also of colloids, particularly of plasma albumin. Diminished circulation is shown by the narrowing of the glomerular capillary lumina, due to the familiar hyaline thickening of the capillary basement membranes, to endothelial proliferation, and to deposit of hyaline material in the lumina. In very early acute nephritis, when these phenomena may not be striking, the distended congested capillaries nevertheless indicate an inflammatory stasis which, in fulminant cases, may be practically complete. Also, latterly, in subacute nephritis, the presence of epithelial crescents adds to the mechanical difficulties, both by compressing the tuft and by obstructing the neck of the tubule. On the other hand, while such active inflammatory changes tend to diminish total filtration, they, here as elsewhere, naturally make the capillaries less selective membranes, and permit the passage of albumin from the plasma, as in inflammatory exudates.

If we run through the chief clinical findings in acute and subacute nephritis we see that these key changes in the glomeruli account for the greater part of the whole picture.

Albuminuria, first of all, is much too considerable to be entirely accounted for by the cells and debris of the deposit, and exudation of protein from the blood stream seems to be the only feasible explanation. The inflamed hyperpermeable glomeruli are obviously the most likely site for this leakage. In the same way *haematuria* is evidently chiefly from inflamed glomeruli. Some hyaline *casts*, and the matrix of some other casts, doubtless represent coagulated exudate from glomerular capillaries. Others, such as epithelial casts, bear evidence of their tubular origin; and even hyaline casts have been shown repeatedly in process of formation from desquamated tubular cells. On the whole, casts are probably less predominantly of glomerular origin than is albuminuria.

Where *oliguria* accompanies a rising blood urea, diminished filtration through the obstructed glomeruli is the probable cause. Diminished total filtrate is bound to lead to proportionate oliguria, provided there is a normal degree of reabsorption in the tubules. In the oliguria of acute and early subacute nephritis tubular reabsorption, as measured by the concentration of the urine, is often practically unimpaired; but at least it is not more active than normally, so that excessive reabsorption does not explain the oliguria. In markedly oedematous cases, of course, the oedema and the diminished filtrate are related, but the exact nature of this relationship is one of the most difficult problems of nephritis. Could inability of the kidneys to excrete water, or salt and water, of itself lead to oedema, in spite of the alternative routes of elimination by skin and bowel, etc.? While established oedema can frequently be varied to a remarkable degree by altering the amount of available salt, retention of sodium chloride alone can scarcely be the sole cause of oedema, for cases with extreme salt retention may not show it[1]; nor, indeed, does water retention necessarily lead to oedema, for complete anuria may occur without it. These are suggestive facts, though Shaw Dunn,[2] in a recent paper, has shown that they are not conclusive evidence against inadequate excretion of salt and water by the kidneys being the cause of oedema. Of other suggested factors, altered permeability of the capillaries throughout the body and lowered colloid osmotic pressure in the blood due to albuminuria[3] are prominent. Of the two, increased capillary permeability would seem to play the more important part in acute and subacute nephritis, and it may be assisted by a raised capillary blood pressure. The more highly albuminous content of the oedema fluid of acute nephritis and other active nephritis has been demonstrated,[3 4 5] and tends to show that the capillary wall is no longer permeable only to crystalloids. That histological examination does not show generalized capillary changes[6] does not in itself disprove the view, for abnormality of function is by no means always indicated by evident histological changes. There is some reason to think that there may be some allergic effect on the glomerular capillaries in nephritis, and, if that is so, it may well be that the capillaries generally also suffer a lesser degree of damage, not obvious histologically, in the most active phases of nephritis.

The raised *blood pressure* is another of the more difficult of the associated disturbances in nephritis, and perhaps it would be wisest simply to admit that we do not know its cause. We know that, with a few exceptions, it is present in all sorts of cases of renal disease when there is some insufficiency, and is absent when there is none. The exceptions include some cases of waxy disease with renal insufficiency, some cases of polycystic kidney, some prostate cases, cases of symmetrical cortical necrosis, etc. We have to decide whether to emphasize the relationship itself or its inconstancy. Are we to hold that the exceptions prove that hypertension cannot be the direct